PATHOPHYSIOLOGICAL REACTIVITY OUTLINED VIA ALGORHYTHMIC NETWORKS AND ETIOPATHOGENETIC CLUSTERS FITS THE CRITERIA OF GRAPH THEORY

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Contemporary medicine is faced with a challenging need of transformation both in learning/teaching methodology and cognitive aspects of physiology. Due to explosive increase of the volume of potentially relevant information and nonlinearity of biological reactivity, understanding of a nature of human body performance in health and disease has become a growingly complex. Classical reduction of disease phenomena to a singular analytical pathway has become insufficient. Multiple new pathways (parallel, feed-forward, branching, etc) have come into focus in considering etiology, pathogenesis, manifestations and outcomes of disease states. A plethora of measurable data ("big data") has still been waiting for a proper integration (Figure 1). Beyond the glittering surface of modern technologies (research and diagnostic ones) there is a struggle for a more complete cognitive prospective and comprehensive vision of human body life processes. Understanding of pathophysiological pathways and networking has emerged as urgent issue not only to students ant their teachers but to researchers and physicians, as well. Pathophysiology anchoring mission and position within the cognitive landscape requires methods, professionals and academic strategy to cope efficiently with contemporary demands (health providers, societal, etc) (Figure 2). The next generation's learners should increasingly be able to extract and synthesize knowledge. With support of powerful information technology training and coaching of a newcomer should be channeled towards such goals. General academic strategies include policies of outcome based programs, a narrowing of the clinical and bench research, building theoretical and practical capacity to integrate scientific knowledge and clinical experience, nurturing a critical inquiry attitude, and learner's ability to self-evaluate and later self-regulate in clinical practice.

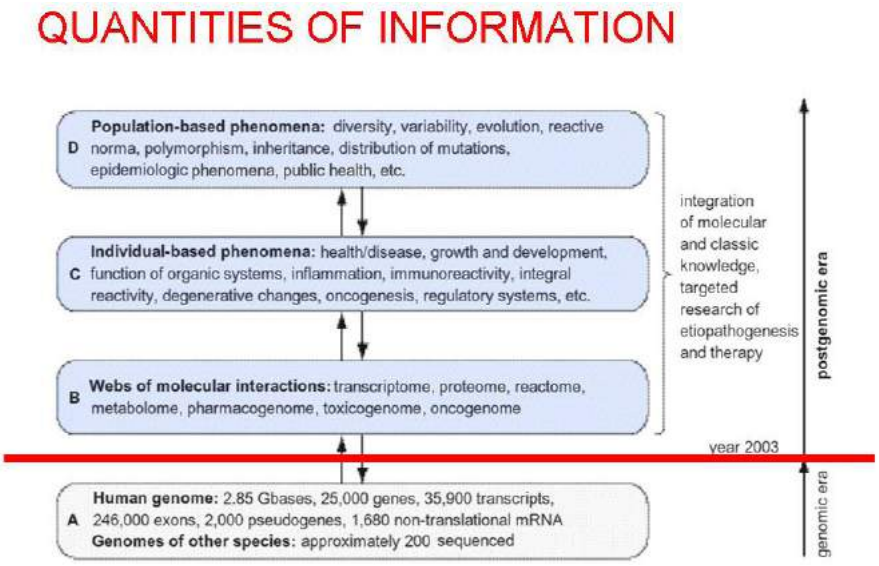


Figure 1. Classical clinical and epidemiological knowledge (source levels C and D) are enriched by exploding quantities of molecular data (source levels A and B) in postgenomic era. Presently big data of molecular information dominantly represents a "raw material" to be integrated within a reinterpretation of human body physiology and pathophysiology

In order to upgrade the understanding of disease phenomena we have developed two methods, matrix-driven algorhythmic elaboration of disease pathways and case-based etiopathogenetic clusters. **Algorhythmic elaboration** enforces the horizontal, vertical and longitudinal integration of patient relevant information. The pathways and networking of processes are crystallized out of plethora

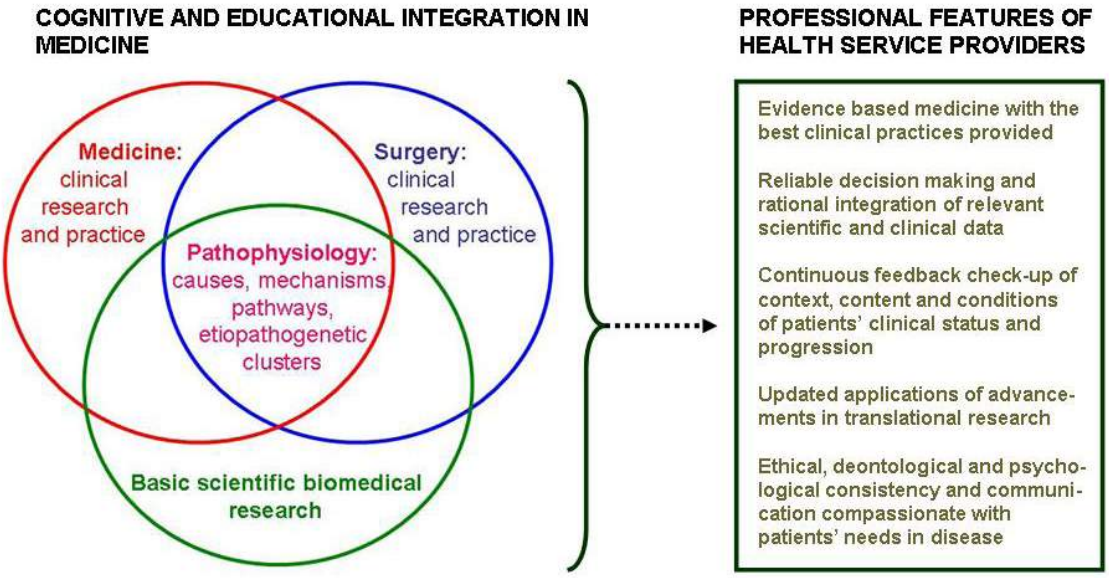


Figure 2. Educational and cognitive advancements are critical for tomorrow medical providers. Venn diagram puts pathophysiology into anchoring position within the three major activities and resources of the science medicine. The fulfillment of practical role of physicians and other health professionals heavily relay on both research and practice as major sources of knowledge

of clinical data (signs, symptoms, hidden dysfunctions, outcomes, etc) and knowledge of sub-systems (nano-molecular, thermal, macromolecular, genomic expression, cellular phenomena, etc.), which are largely acquired via reductionistic methodologies. The method consists of the four layers (Figure 3). Learner is led to analyze and to re-synthesize the architecture of underlying etiopathogenesis. Ex-

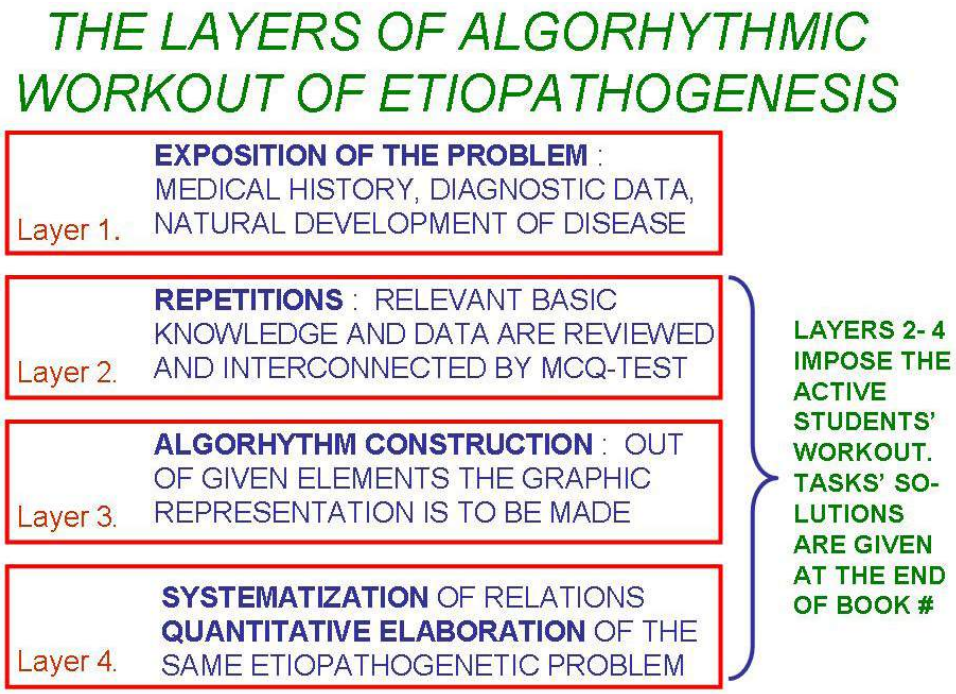


Figure 3. Four layers of algorhythmic analysis and resynthesis. The stepwise method of etiopathogenetic algorhythms provide and enforces the active students' participation in teaching/learning procedure. It is an open, self-controlled approach, in which a newcomer is led by the matrix of the task through 4 interconnected layers. Analysis, repetitions from various angles, re-synthesis of unit-elements, and quantitative consideration are systemically put together in teaching/learning procedure.
Abbreviations: MCQ, multiple choice questions.
 # Z Kovač et al. Pathophysiology. Study Guide Algorhythms – Problem Solver. Book Two. Medicinska naklada Zagreb 2014

position of problem in form of "raw data" is primarily qualitative type of information, usually from patients' history. Repetitions of relevant knowledge re-enforce understanding of given case manifestations within a broader context of relevant knowledge. Algorhythmic workout represents an active build-up of cause-consequence pathways of events out of pre-given 25-30 units of etiopathogenesis. Graphic symbolic representation outlines positive and negative feedback loops, as well as parallel and contextual events. Systematization and quantitative aspects contribute to a more comprehensive and contextual interpretation.

Algorhythmic pathophysiology elaboration has revealed a natural tendency to form common crossing points of reactivity of heterogeneous pathways. The pathways spontaneously converge and form **etiopathogenetic clusters (EPCs)**. EPCs integrate multiple inputs and multiple exits. They look like natural integrators, the common „hubs" of human body response in various diseases (Figure 4). 91 EPCc have been identified at multiple levels of hierarchy of human body disease reactivity. EPCs are shared in natural development of heterogeneous conditions and they show tendency to form a network (Figure 5). Among the EPCs connecting pathways serve as "the ECP-driving force". Thus, the EPCs may be seen as "a new emerging feature" of pathophysiology foundation of disease. Case study approach within the EPC-context simplifies consideration of 32,000 diseases/disorders listed within human medicine agenda.

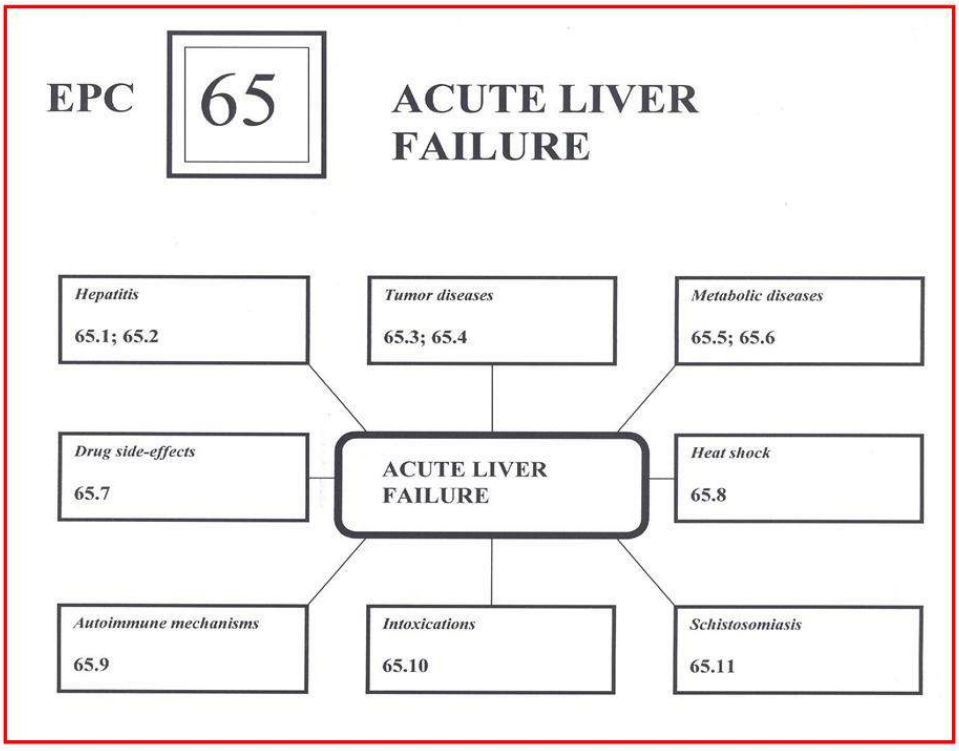


Figure 4. Introductory rosette of the EPC of acute liver failure serves as navigation scheme among multiple groups of conditions. Decimal numbers are codes which connect the rosette with the individual case studies that follows in the structure of the book. Each cluster out of 91 EPCs has such belonging rosette in a form of undirected graph representation. (Z Kovač et al. Clinical Pathophysiology - Etiopathogenetic Clusters (4 Volumes). Medicinska naklada, Zagreb 2013.)

Physicians' approach to whole body will always remain the major referent concept and orientation in medicine, despite a progressive compartmentalization into narrow fields of interest (specializations, sub-specializations). Algorhythms and EPCs may be considered as a counter-response to the real challenge of the plethora of information. Clinical medicine and biomedical research are two major pillars for the integrative physiology. Bridging the basic science – clinical application gap, provided by the two methods, may help redesigning and upgrading of curricular contents. One example is schematically outlined in Figure 6. They improve efficiency of teaching/learning and navigate towards a deeper understanding of etiopathogenesis. Two methods may be useful to students,

researchers and physicians in attempts to cross the major epistemological problem (reductionism versus integral view) in dealing with complexities of human body reactivity. On the other side, two approaches have applied a symbolism of **graph theory** to the real etiopathogenetic relations. Graph theory is useful concept for nonlinear complex systems. Directed links in-between elements of algorhythm do indicate a "physiological flux", mutual oriented influence, and/or cause-consequence relations (see Figure 5). Graphic outline also forms tree-like branching points in etiopathogenetic pathways' networking. Undirected links in the EPC- rosette serve as indicator of certain, non-specified type of association (see Figure 4). Spontaneous networking of disease processes, pathways and EPCs, presented with help of graph theory symbolism may facilitate our understanding of throughput biological data. The upcoming era of medicine seeks for more efficient cognitive and educational armamentarium. These two methods may be useful in bridging the gaps of contemporary medicine.

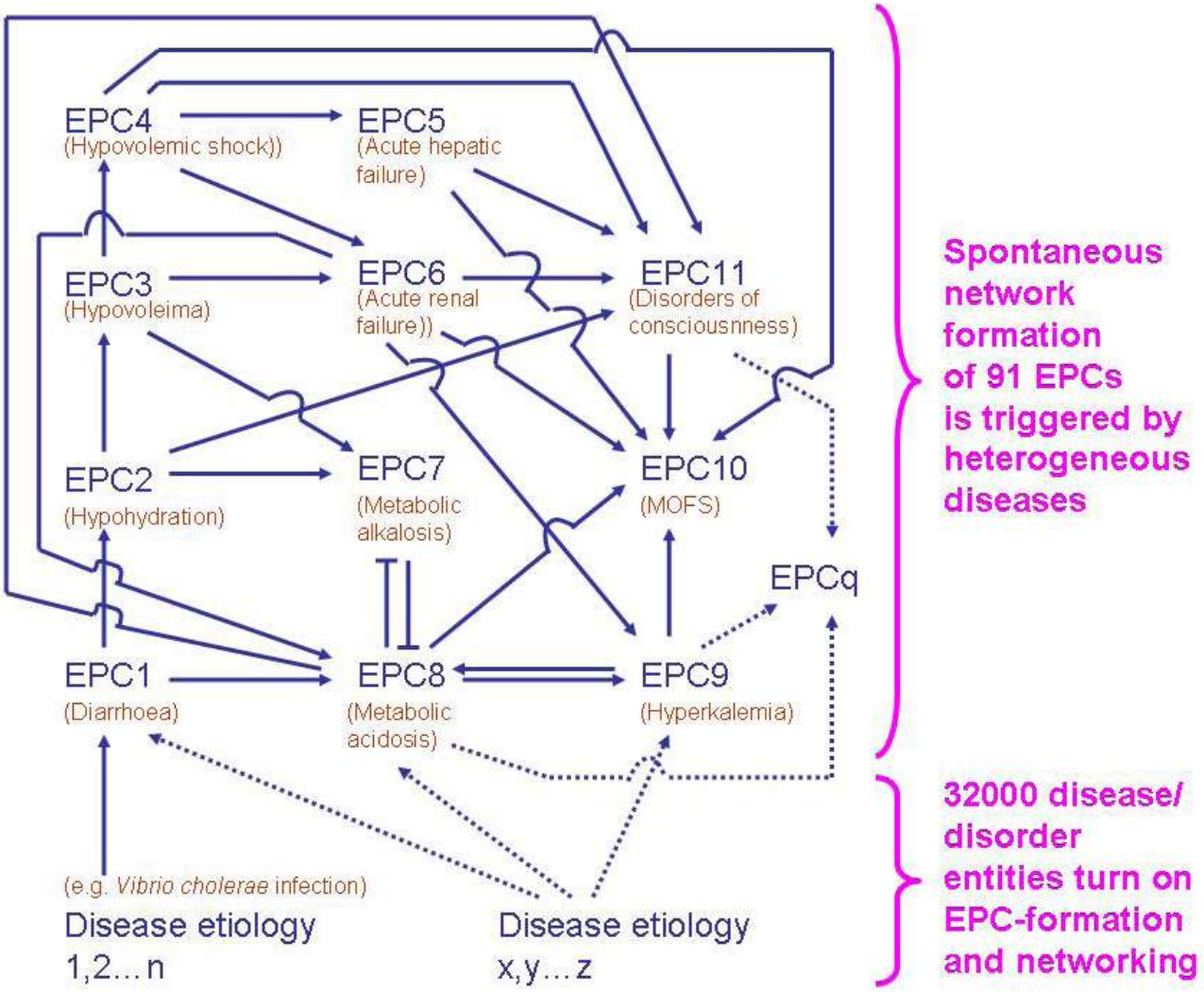


Figure 5. Multiple nosologies (the etiopathogenesis of individual disease entities) spontaneously trigger the EPC-network formation represented by directed graph relations among clusters. In parentheses the example of cholera development is outlined. The insights into etiopathogenetic EPC networking may help both physicians and researchers in their appreciation of systemic nature of pathobiology of disease/disorders.
Abbreviations: EPC, etiopathogenetic cluster; n,x,y,z – any real number of 1-32000; q-any real number of 1-91

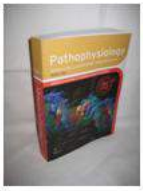
Level 1.Systematization, didactic hierarchy, data bases, concepts, natural laws, visions

Reasoning and knowledge processing:

Top – down approach, deductive, hypothetical, holistic, probabilistic, ignoring unfitting data, often descriptive pheno-menology approach

Level 2. Problem solver – four layer matrix guided study, real measured data

Reasoning and knowledge processing:



Contextual bench-marking, active agorhythmic resynthesis, self controlled process, inducti-ve/deductive, qualitative and quantitative dimension of patient problem, networking of disease pathways outlined and reconstructed

Level 3. Etiopathogenetic clustering - the case study problem solver

Reasoning and knowledge processing:

Bottom-up pathway, practical, casuistic with high variability, unique patients' manifestations' consideration, self controlled, often faced with unexpected features

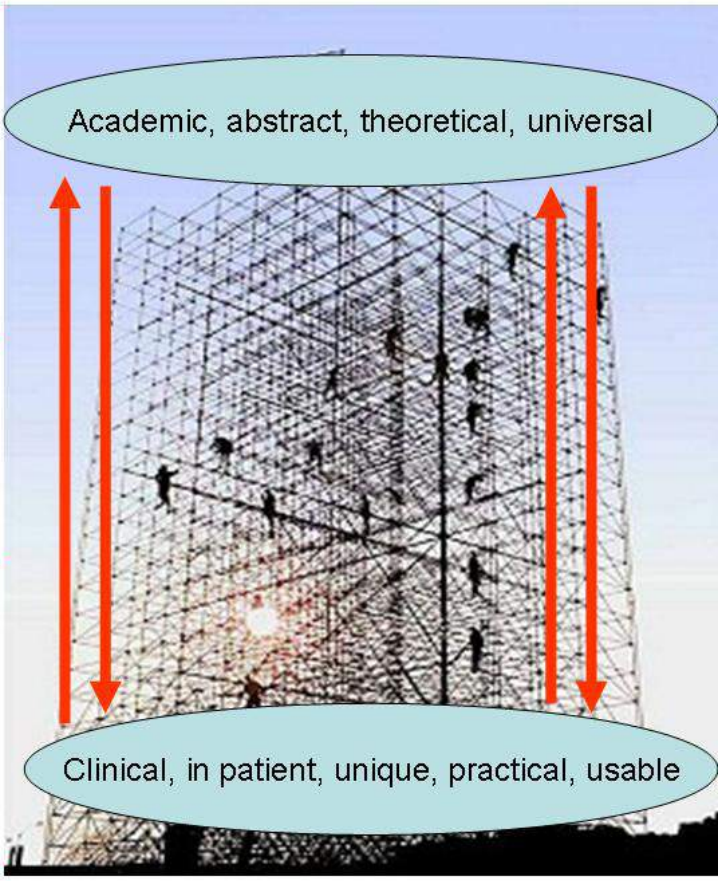


Figure 6. Zagreb School of Pathophysiology elaborates curricular subject contents by using three different teaching/learning and knowledge processing standpoints. Written materials are designed in a way to enforce an active student participation and integration of clinical and theoretical dimension of disease. Two methods are useful in bridging heterogeneous facets and quality of information